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THE PERMANENCE OF THE SCHICK NEGATIVE STATE.

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IT is customary to assume that the state of immunity to diphtheria which is indicated by a negative Schick test is permanent. This is suggested by much experimental work on the duration of active immunity, but, because modern methods of diphtheria prevention are of such recent date, it is impossible to examine the expectation by actual experience in human beings. This paper records the results of retesting children at intervals after a negative Schick test was obtained, the maximum interval being seven years. An investigation has also been made of the capacity of response to artificial immunisation of any who may have become positive after having once been negative. 973 children were retested one to seven years after the first negative Schick test. All were negative with the exception of 28 (2·9 per cent.). 541 children were retested after one to three years, 191 after three to five years, and 241 after five to seven years. After one to three years the percentage of positives was 2·6, after three to five years 5·3, and after five to seven years 1·7, differences which are probably not significant.

The 973 children may be subdivided into two groups—viz., 533, who were negative to the original Schick test one to seven years previously, and 440, who were positive on the original Schick test and became negative only after injections of prophylactic mixtures (vide table). 527 children (98·9 per cent.) of the 533 who were negative on the original Schick test one to seven years previously were read as negative on retest, and 6 (1·1 per cent.) as positive. 418 (95 per cent.) of the 440 in the immunised group were negative on retest and 22 (5 per cent.) were positive. It will be seen that there is little difference in the Schick-positive rate of the two groups. Further tests may, however, confirm the observation that children who have been immunised by artificial methods show a somewhat higher percentage of positives on retest than those who have become immune in response to the weaker stimuli which they may receive naturally. It may be possible that some individuals can be immunised only by the larger stimuli introduced in prophylactic mixtures, and that these people are prone to lose some of the antitoxin

they may thus with difficulty acquire. One or two individuals who gave faint reactions may have been wrongly read as positive in our recent retesting, but it is better to read as positive one or two doubtful reactors who are really immune than to pass as Schick-negative a susceptible subject. The Schick level of immunity corresponds to about 1/100th to 1/30th of a unit of antitoxin per c.cm. of blood. The Schick-negative reactor contains more than this amount and the Schick-positive reactor less.

Group 1.—533 Children Negative on Original Test.

In six children who were originally Schick-negative one to seven years previously a positive Schick result was obtained, indicating a quantity of antitoxin less than 1/50th of a unit per c.cm., but four of the six became negative within a brief interval of the Schick test injection. Thus, two weeks after the Schick test was made, a blood sample from one child was examined and found to contain half a unit per c.cm. Blood samples from two other children contained 1/10th unit of antitoxin per c.cm. within one week of the Schick injection, and a fourth child had 1/100th unit in two weeks and gave a Schick-negative reaction in three weeks. Only 2 (0·4 per cent.) of the children (italics in table) required an injection of an immunising mixture. One had no detectable antitoxin in seven days, was given an immunising injection of toxoid-antitoxin at 14 days, had 1/100th unit at 21 days, and was definitely negative a fortnight later. The other gave a positive reaction to a second re-Schick one week after the first, had less than 1/1000th unit of antitoxin, and was given 1·0 c.cm. of an immunising mixture after two weeks and had 1/250th unit of antitoxin in four weeks. This child has recently had another 1·0 c.cm. dose of a prophylactic mixture and is still under observation.

The first four cases afford a parallel to the experiments of Glenny and Allen (1922) on rabbits and guinea-pigs ; they found that even 1/20th of a Schick test dose might act as a " secondary stimulus " (Glenny and Sudmersen, 1921), causing a rapid production of antitoxin in an animal which had once been actively immune but which had subsequently lost some or all of its circulating antitoxin. The present investigations have amply confirmed Glenny's observations, and there is no room for doubt that such a small amount of toxin as 1/50th of the guinea-pig minimal lethal dose has a pronounced influence on the amount of circulating antitoxin actively produced, even of such a large animal as a human being. This point has already been discussed by O'Brien (1926), who instanced six cases in which a Schick test dose produced a demonstrable rise in antitoxin in actively immune subjects. Similar observations have been made by Kellogg and Stevens (1927).

Group 2.—440 Children Positive on Original Test and Negative immediately after Immunisation.

Twenty-two children (5 per cent.) in this group were positive on retest one to seven years later, but, as in the first series, all but 2 (0·4 per cent.) developed antitoxin rapidly in response to the stimuli of Schick injections. It will be seen from the table that five of the children were still positive or partially positive on a second re-Schick in the second or third weeks, but one week later all five had 1/25th to 1/5th unit of antitoxin. Two reactors who were more refractory (italics in table) were a brother and sister at a poor-law institution who had been very difficult to immunise in 1925. They had both required two courses of diphtheria prophylactic mixture—six injections of 1·0 c.cm. in all—but were, we think, undoubtedly Schick-negative

finally, the boy within two months and the girl within four months of the last immunising injection. We are confident that the toxin dilutions with which these tests were made were of satisfactory potency on both occasions. On retest three years later both children were positive, and after one week and four weeks had no detectable antitoxin in the blood (i.e., less than 1/2000th unit per c.cm.). Schick tests in the first and fourth weeks were also positive. In the fifth week they were given 1 c.cm. of toxoid-antitoxin mixture. Two weeks later the boy had 1/25th unit of antitoxin, indicating a fairly brisk response, but his sister still remained refractory and is receiving further injections.

Discussion.

It will be seen that there is very little difference between the two groups, which can now be considered together for purposes of discussion. At first sight the percentage of children who had reverted to the Schick-positive state after having once been negative is disquieting ; 28 children (2·9 per cent.) of 973 who had been read as negative one to seven years previously were regarded as positive on retest. It is, however, reassuring that only four children (0·4 per cent.) required immunising injections, and that three of the four showed a marked rise in antitoxin within one to three weeks of a single dose of prophylactic mixture. It is doubtful, therefore, if the immunising mechanism of these children would really have been sluggish vis-à-vis an average infecting dose of virulent organisms. The fourth child (0·1 per cent. of the entire series) is in a different category, for she failed to show the slightest response to an injection of 1·0 c.cm. of toxoid-antitoxin mixture.

The efficiency of the Schick dose of toxin as a " secondary stimulus " is remarkable. It is a very small amount of toxin, originally founded on 1/50th of the guinea-pig minimum lethal dose, and in combining power is equivalent to 1/1000th of a unit of antitoxin. If, however, a Schick-negative reactor has lost some of his antitoxin and becomes Schick-positive, with little or no detectable antitoxin, the Schick dose of toxin may be sufficient to make him once again Schick-negative. In other words, active immunity with the capacity for responding to a fresh stimulus has remained, although circulating antitoxin may have been lost. The fact that a Schick dose of toxin may be capable of stimulating the production of circulating antitoxin in an actively immune subject must be borne in mind in connexion with every type of experiment, in animals as well as in human beings, in which serial Schick tests are used for the study of changes in immunity.

Over and above the series under review we have retested a group of 194 children who were negative on the original test three months previously. All were negative on retest.

The observations, so far as they go, while not completely establishing the dictum " once Schick-negative, always Schick-negative," support the more general statement " once immune, always immune," if by immunity we imply a more ready protective response to the invasion of the specific

toxin. One would expect such a "potential" immunity to be sufficient to protect an individual against any serious infection by the diphtheria bacillus.

Tests on 973 Children.

After 1–7 years: re-Schick.			Weeks after re-Schick.					
			1	*2*	*3*	*4*	*5*	*7*
533 children negative on original Schick test.	−527 (98·9 %)	1	..	1/2*	..	..	..	..
		2	1/10	..	..	..	..	..
	+6 (1·1 %)	1	..	1/100	—	..	..	..
		1	*Nil*	*M*	*1/100*	..	—	..
		1	+	*1/1000*	..	*1/250*	(*a*)	..
			..	*M*	..	..	..	..
440 children positive on original Schick test and negative immediately after immunisation.	−418 (95·0 %)	2	1/2	..	..	..	..	..
		1	1/50	1/25	1	..	..	..
		2	1/100	..	..	1/25	..	..
		1	1/100	—	..	..	..	..
		1	..	1/100	—	..	..	..
		2	..	1/100	±	1/25	..	..
		2	1/250	1/50	..	..	..	..
		1	1/250	..	—	..	..	..
		1	..	1/250	1/5	..	..	..
	+22 (5·0 %)		..	+	..	..	..	..
		1	1/500	..	..	1/50	..	..
		2	..	1/750	1/5	..	..	..
			..	+	..	..	..	..
		1	1/1000	..	—	1/25	..	..
		1	—	..	..	..	..	..
		2	±	—	..	..	..	..
		1	*Nil*	..	..	*Nil*	*M*	*1/25*
			+	..	..	+	..	..
		1	*Nil*	..	..	*Nil*	*M*	*Nil*
			+	..	..	+	..	(*a*)

* = Half a unit of antitoxin per c.cm. of patient's blood.
(*a*) Further details incomplete.
M = Toxoid antitoxin mixture −1·0 c.cm.
+, ±, −, = Reaction to Schick test.

Summary.

(1) 533 children who were Schick-negative on the original test were retested one to seven years later, and showed a 1·1 per cent. Schick-positive rate.

(2) 440 children who were Schick-positive on the original test were rendered Schick-negative by immunisation. When retested one to seven years later 5 per cent. were found to be positive.

(3) In both these groups nearly all the "relapsed" Schick-positive individuals rapidly produced circulating antitoxin in response to very small amounts of diphtheria toxin, and could be considered as in a state of active immunity.

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